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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/527,525

10/14/2005

Athina Markou

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EXAMINER

CARTER, KENDRA D

ART UNIT

PAPER NUMBER

1627

MAIL DATE

DELIVERY MODE

12/15/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/527,525	Applicant(s) MARKOU ET AL.	
	Examiner KENDRA D. CARTER	Art Unit 1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 August 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,6,7,9,16,17,19,27,28 and 32 is/are pending in the application.
- 4a) Of the above claim(s) 10,14,15,17 and 19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,6,7,9,16,27,28 and 32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/22/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The Examiner acknowledges the applicant's remarks of August 31, 2009 made to the office action filed June 24, 2009. Claims 1-3, 6, 7, 9, 10, 14-17, 19, 27, 28 and 32 are pending. Claims 4, 5, 8, 9, 11-13, 18, 20-26, 29-31 and 33 are canceled. Claims 10, 14, 15, 17 and 19 are withdrawn. Claims 1-3, 6, 7, 19 and 27 are amended.

For the reasons in the previous office action and below, the Applicant's arguments of the following 35 U.S.C. 103(a) rejections were found not persuasive, thus the rejection is upheld: 1) claims 1-8, 16, 20, 21 and 29 as being unpatentable over Adam et al. in view of Corsi et al. or Chimulera et al.; and 2) claims 9, 22, 27, 28, 32 and 33 as being unpatentable over Chiamulera et al. in view of Adam et al. as applied to claims 1-8, 16, 18, 20, 21 and 29 above. Both rejections are modified in light of the cancelled and amended claims.

Due to the amendments to the claims the modified 35 U.S.C. 103(a) rejections are made below. Applicant's arguments are addressed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

(1) Claims 1-3, 6, 7 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adam et al. (US 6407,094 B1) in view of Corsi et al. (US 2003/0195139 A1) or Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874).

Adam et al. teaches compounds that act as Group II (i.e. mGluR 2 and 3) metabotropic glutamate receptor antagonist (see column 16, lines 47 and 48) and treat conditions such as nicotine addiction, and opiate addiction (see column 1, lines 54-56

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and column 3, lines 20-24; addresses claims 1-3, 6, 7 and 16). The antagonist can be in their pharmaceutically acceptable salts (see column 3, line 4).

Adam et al. does not teach an antagonist which modulated metabotropic glutamate receptor 5, or its administration in combination with the antagonist of Adam et al.

Corsi et al. teaches a method of treating substance dependence, wherein the substance is nicotine, opiate, cocaine, amphetamine, benzodiazepine and ethanol, comprising administering a therapeutically effective amount of an antagonist of mGluR5 (see claims 21-23; addresses claims 1-3, 6, 7 and 16). The compounds can be in the form of salts (see page 3, paragraph 55, lines 1 and 2).

Chiamulera et al. teaches the significant contribution of mGlu5 receptors to the behavioral effects of cocaine addiction (see page 873, column 1, paragraph 1, last 4 lines). A decrease of self-administration of cocaine was observed with an administration of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP); see page 873, column 2, last paragraph, lines 1-4).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Adam et al. and a combination with an

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antagonist which modulates metabotropic glutamate receptor 5 because of the following: (1) Adam et al., Corsi et al., and Chiamulera et al. teach methods that treat addictive disorders; (2) Adam et al. teaches the treatment of addictive disorders with a mGluR 2 and 3 antagonist; and (3) Corsi et al. and Chiamulera et al. teach the treatment of an addictive disorder with a mGluR 5 antagonist. One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat addictive disorders. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

(2) Claims 9, 27, 28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874) in view of Adam et al. (US 6,407,094 B1) as applied to claims 1-3, 6, 7 and 16 above and Applicant's admitted prior art (see specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4).

The teachings of Chiamulera et al. and Adam et al. all are as applied to claims 1-3, 6, 7 and 16 above.

Chiamulera et al. and Adam et al. do not teach the antagonist 2S-2-amino-2-(1S,2S-2carboxycyclopropane-1-yl)-3-(xanth-9-yl)propionic acid (LY341495; claims 9 and 28). Also, the administration comprising: (a) administering to a subject in need thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5 (specifically LY341495 or/and MPEP) during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal and/or depression, is not taught (claim 27). Lastly, wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously is also not taught (claim 32)

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and the antagonist LY341495 because of the following: (1) both Chiamulera et. al. and Adam et al. teach methods to treat substance abuse; (2) Adam et al. teaches the treatment of an addictive disorders or depression with a mGluR 2 and 3 antagonist; and (3) LY341495 is a well

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known mGluR 2 and 3 antagonist in the art (indicated by the specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4). One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat substance abuse. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and an administration comprising: (a) administering to a subject in need thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5 (specifically LY341495 or/and MPEP) during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal

and/or depression; or (c) wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously because without unexpected results, one skilled in the art can reasonably design the period of administration.

Response to Arguments

The Applicant argues that there is neither experimental data nor plausible substantiation in Adams et al. to suggest that the compounds are indeed effective to treating drug dependence. More importantly, as explained below, the pure speculation of Adams et al. is contradictory to results from actual scientific studies that were published in peer reviewed journals. At the time of invention, several research groups have shown that agonists (not antagonists) of mGluR2/3 were able to attenuate withdrawal symptoms and to treat morphine or nicotine dependence. Further, Fundytus et al. results show a preventative effect of the antagonist, and not efficacy in treating withdrawal if the antagonist is administered after the development of dependence. Thus, the reference teaches away from combining mGluR2/3 antagonist and a mGluR5 antagonist as presently claimed.

The Examiner disagrees because first Adams et al. is a US Patent, which is believed to be enabled by its disclosure. In regards to the other art showing opposite results, the teaching of Kenny et al. (provided by Applicant's 8/31/09 in arguments) can help to explain the differences. Particularly, Kenny et al. teaches on page 1075, column 1, paragraph 3, that prolonged continuous nicotine exposure increase mGluR1 receptor function, but repeated exposure to psychostimulants decreased mGluR1 function. Thus, it

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is possible that chronic nicotine and psychostimulant administration induce different alterations in glutamatergic transmission. Alternatively, this apparent discrepancy may be explained by the fact that the long-term behavioral effects of drugs of abuse are related to the dosing administration regimen. In regards to the teaching away of Fundytus et al., the Examiner still believes that Fundytus et al. provides a means of attenuating withdrawal symptoms (i.e. reducing withdrawal symptoms) by administering the non-selective antagonist MCPG (see page 1018, column 2, discussion, lines 1-6; and page 1017, column 1, paragraph 3 in its entirety, Figure 1b). Thus, the non-selective mGluR antagonist MCCG (at receptors 1, 2, 3, and 5) was effective in treating withdrawal symptoms. The art provided in the rejections above support the Examiner's arguments.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 9:00 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kendra D Carter/

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627